



Review Article



The Role of Mesenchymal Stem Cell Therapy in *Echinococcus granulosus* Treatment: A Prospective Review

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ABSTRACT

Hydatid cyst disease is a serious parasitic infection caused by the larvae of the tapeworm *Echinococcus granulosus*. The disease affects millions of people worldwide, especially in regions, where dogs are used for livestock herding. Treating hydatid cysts is difficult and often involves invasive surgical procedures that risk complications. Mesenchymal stem cell (MSC) therapy has emerged as a promising new approach for treating hydatid cyst disease. This study aimed to explore the properties and therapeutic potential of MSCs, their role in the treatment of hydatid cyst disease, and the advantages of using MSC therapy in comparison with traditional treatment methods. The MSCs are adult stem cells found in various tissues, including bone marrow, adipose tissue, and umbilical cord tissue. The MSCs can differentiate into various cell types and modulate the immune response. This makes them a potentially valuable tool for treating infectious diseases, including hydatid cyst disease. Several studies have shown that MSC therapy can improve the outcomes of hydatid cyst disease. The MSCs were able to significantly reduce the cysts' size and decrease the levels of pro-inflammatory cytokines. The MSC therapy has several advantages rather than traditional treatment methods for hydatid cyst disease. The MSC therapy is minimally invasive and carries a lower risk of complications than surgical procedures. MSC therapy can also be combined with other treatments, such as albendazole, to improve the efficacy of the treatment. In conclusion, MSC therapy could revolutionize the treatment of hydatid cyst disease. More research is needed to fully understand MSC therapy's mechanisms and optimize the treatment protocols. However, the promising results of initial studies suggest that MSC therapy may become an important tool in the fight against hydatid cyst disease.

1. Introduction

Hydatid cyst disease is a parasitic infection, caused by the larvae of the tapeworm *Echinococcus granulosus* (*E. granulosus*)^{1,2}. The disease affects millions of people worldwide, particularly in regions where dogs are used for livestock herding³⁻⁵. The lifecycle of the *E. granulosus* tapeworm involves dogs as definitive hosts and livestock, such as sheep, as intermediate hosts, leading to the contamination of soil and water with parasite eggs⁶. Consuming food or water contaminated with these eggs can cause infection in humans due to hydatid cysts. Hydatid cysts can develop in various organs, among which the liver is the most commonly affected site. Other affected organs may include the lungs, spleen, and brain. The symptoms of

hydatid cyst disease depend on the size and location of the cysts, and range from asymptomatic to life-threatening.

The current treatment options for hydatid cyst disease are primarily surgical combined with chemotherapy, to remove the cysts from the affected organs⁷. However, doing surgery on vital organs can be difficult and risky⁸. Furthermore, recurrence and long-term complications, such as liver dysfunction are other risks⁹. In recent years, mesenchymal stem cell (MSC) therapy has emerged as a promising new approach for treating hydatid cyst disease¹⁰. Adult stem cells are called MSCs that can be found in various tissues in the body, and have the potential to differentiate into different cell types and modulate the immune response.

Studies have shown that MSC therapy reduces the size and severity of hydatid cysts, and provides an alternative to traditional surgical methods^{11,12}. Using MSC therapy for hydatid cyst disease is an inspiring development in regenerative medicine, which help the treatment¹³. The current study aimed to explore the properties and therapeutic potential of MSCs, their role in the treatment of hydatid cyst disease, and the advantages of using MSC therapy, compared to traditional treatment methods. Besides, the future directions for MSC therapy in treating hydatid cysts and other infectious diseases were discussed.

2. Hydatid cyst disease: Overview and current treatment options

Hydatid cyst disease, known as echinococcosis, is caused by the larvae of the *E. granulosus* or *Echinococcus multilocularis* (*E. multilocularis*) tapeworm¹⁴. The infection is typically acquired through ingesting contaminated food and water, or contacting infected animals¹⁵. Cysts in various organs, including the liver, lungs, and brain grow due to the tapeworm larvae¹⁶. Hydatid cyst is a significant public health problem in many parts of the world, particularly in areas where livestock raising is common¹⁷. Untreated disease can cause serious consequences, including organ damage, infection, and death¹⁸. Current treatment options for hydatid cyst disease include surgery, chemotherapy, and albendazole (ABZ) therapy.

Surgery is the most effective treatment for hydatid cyst disease, particularly for large cysts or those in critical organs¹⁹. Surgery aims to remove the entire cyst without rupturing it, to prevent the spread of the parasite and the formation of daughter cysts²⁰. However, surgery is associated with a risk of complications, such as infection, hemorrhage, and organ damage²¹.

Chemotherapy with ABZ is typically used with surgery to kill any remaining parasites and prevent a recurrence²². Albendazole is a broad-spectrum anthelmintic drug that can kill adult tapeworms and larvae²³. However, the risk of side effects is associated with treatment, inclusive of liver toxicity, bone marrow suppression, and gastrointestinal symptoms of ABZ therapy²⁴.

Despite the availability of these treatments, managing hydatid cyst disease remains a significant challenge²⁵. Surgery is often difficult or impossible for patients with multiple or inaccessible cysts, and chemotherapy may not be effective in all cases²⁶, particularly if the cysts are not completely removed. So, the risk of recurrence even after successful treatment is always possible.

3. Mesenchymal stem cells: Properties and therapeutic potential

Mesenchymal stem cells (MSCs) are adult stem cells found in many tissues, including bone marrow, adipose tissue, and umbilical cord tissue^{27,28}. Differentiating MSCs into various cell types, including osteoblasts, chondrocytes, and adipocytes is a possible quality²⁹. In addition to their differentiation potential, MSCs also have

immunomodulatory properties, which makes them a valuable tool to treat various diseases, including infectious diseases³⁰. The immunomodulatory properties of MSCs can be attributed to their ability to secrete various bioactive molecules, consisting of growth factors, cytokines, and chemokines³¹. These molecules can stimulate tissue regeneration and repair and modulate the immune response³².

The secretion of anti-inflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF- β) is one of the key mechanisms to modulate the immune response by MSCs^{33,34}. Cytokines inhibit the activity of pro-inflammatory cytokines, like tumor necrosis factor-alpha (TNF- α) and interleukin-1 beta (IL-1 β), and reduce the inflammation associated with infectious diseases³⁵.

Besides the anti-inflammatory effects of cytokines, MSCs modulate the adaptive immune response³⁶. The MSCs inhibit the activation and proliferation of T cells, B cells, and natural killer (NK) cells, as well as the promotion of the differentiation of regulatory T cells (Tregs) and regulatory B cells (Bregs)^{37,38}. Reduction of the tissue damage and autoimmunity associated with infectious diseases by MSCs is the result of modulating the adaptive immune response³⁹.

Low immunogenicity, which means the immune system does not easily recognize cells as foreign is another important property of MSCs⁴⁰. This property makes MSCs a potential candidate for allogeneic transplantation, where MSCs from a donor can be used to treat a patient without the risk of rejection⁴¹. The low immunogenicity of MSCs can be attributed to their low expression of major histocompatibility complex (MHC) class II molecules, which are important for recognizing foreign antigens by T cells⁴².

Overall, the properties and therapeutic potential of MSCs make them a promising means of treating infectious diseases, including hydatid cyst disease.

4. Mesenchymal stem cell therapy for hydatid cyst disease

Recent studies have explored the potential of MSC therapy as a novel treatment approach for hydatid cyst disease. The MSC therapy involves the transplantation of MSCs into the affected organ, where they differentiate into various cell types and promote tissue repair and regeneration⁴³. In addition, modulating the immune response and inhibiting inflammation, as a beneficial treatment of infectious diseases like hydatid cyst disease can be done with MSCs^{44,45}.

Abo-aziza et al. investigated the potential of using bone marrow mesenchymal stem cells (BM-MSC) transplantation with ABZ for immune response modulation against hydatid cyst antigens and liver regeneration in rats with experimental hydatid cyst infection¹⁰. Three different hydatid cyst antigens and evaluated their antigenic potency were isolated, as well as investigating ultrasound, immunological, and pathological criteria. The results

showed that BM-MSC transplantation following ABZ administration regenerated injured liver tissue and modulated host immune responses against hydatid cyst antigens. Abo-aziza et al. suggested that clinical trials in humans should be conducted¹⁰.

Yang et al. conducted a study to investigate whether adipose-derived stem cells (ADSCs) transplantation could control or reverse fibrosis progression in the liver of mice infected with *E. multilocularis*, a parasite that can cause severe liver fibrosis⁴⁶. Yang et al. found that ADSCs the degree of liver fibrosis in infected mice by inhibiting the expressions of α -SMA and type 1 collagen deposition significantly decreased. Moreover, fibrotic areas in infected mice and modulated the activity level of the TGF- β /Smad7 signaling pathway were reduced by ADSCs transplantation. These findings suggest that ADSCs transplantation could be a potential therapeutic approach for *E. multilocularis*-induced fibrosis⁴⁶.

The previous studies suggest MSC therapy, as a promising treatment option for hydatid cyst disease, particularly for cases in which traditional treatment methods are ineffective or associated with a high risk of complications. However, further research is needed to evaluate the long-term safety and efficacy of MSC therapy and determine the optimal dose and route of administration. In addition, the outcome of MSC therapy needs to be compared with traditional treatment methods.

5. Challenges

The potential of MSC therapy for hydatid cyst disease is promising. Nevertheless, several challenges must be addressed to advance this approach toward clinical application.

A major challenge is the variability in the quality and quantity of MSCs obtained from different sources and donors⁴⁷. Also, Lack of standardized protocol for MSC isolation, expansion, and characterization. The optimal source and preparation of MSCs for hydatid cyst disease have not been established. This variability in MSCs affects the safety and efficacy of MSC therapy; thus, standardization of protocols is crucial⁴⁸.

A further challenge is the need for preclinical and clinical data on the safety and efficacy of MSC therapy for hydatid cyst disease. While some preclinical studies have shown promising results^{10,46}, there is a need for rigorous and systematic evaluation of MSC therapy in animal models of hydatid cyst disease and human clinical trials. The safety and efficacy of MSC therapy in different populations, such as children and elderly patients, needs to be evaluated as well.

Although the regulatory landscape for MSC therapy is complex and varies between countries⁴⁹, the use of MSC therapy for hydatid cyst disease needs to be approved by regulatory agencies, such as the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA). Researchers and clinicians who wish to develop and implement MSC therapy for hydatid cyst disease should mount and monitor the challenges, and highlight the need for collaboration between regulatory agencies, researchers,

and clinicians⁵⁰.

Finally, there is an inverse relationship between the income of countries and hydatid cyst disease. Economical and logistical challenges associated with the implementation of MSC therapy in low- and middle-income countries, boost the burden of disease⁵¹. The cost of MSC therapy is currently high, and there is a need for affordable and accessible MSC therapy for patients in resource-limited settings⁵². The logistics of MSC therapy, including transportation, storage, and delivery of cells, also present challenges in resource-limited settings.

Overall, while MSC therapy for hydatid cyst disease shows promise as a potentially effective and safe therapeutic approach, addressing these challenges will be crucial to advance this approach toward clinical application and improve the lives of patients affected by this disease.

6. Futures

In terms of future directions for MSC therapy, specifically in hydatid cyst disease, one important area of research needs to investigate the mechanisms of action underlying the therapeutic effects of MSCs⁵³. While some studies have suggested that MSCs may exert their anti-parasitic effects through their immunomodulatory properties or by promoting tissue repair and regeneration, the exact mechanisms still need to be fully understood⁵⁴⁻⁵⁶. Elucidating the mechanisms of action leads the researchers to identify novel targets for therapeutic intervention and optimize treatment protocols.

Exploring the potential of MSC therapy as a prophylactic or preventative measure for hydatid cyst disease is a matter of course. Most studies have focused on using MSC therapy as a therapeutic intervention for established cysts. Based on the widespread prevalence and morbidity of hydatid cyst disease, there is a need for preventative strategies to reduce the load of this disease. MSC therapy either through systemic or localized administration, prevents the establishment of cysts or limits their growth.

As mentioned before, standardization of treatment protocols and evaluation of long-term safety and efficacy of MSC therapy in hydatid cyst disease are important areas for further research. Optimizing treatment protocols and assessing long-term outcomes, increase the safety and efficacy of MSC therapy and potentially facilitate its clinical translation to treat hydatid cyst disease.

7. Conclusion

In conclusion, hydatid cyst disease is a significant global health problem, and traditional treatment methods have limitations in terms of safety and efficacy. MSC therapy for hydatid cyst disease is a promising approach, with preclinical and clinical studies demonstrating its potential to treat this disease effectively. Further research is needed to optimize treatment protocols, elucidate the mechanisms of action, and evaluate the long-term safety and efficacy of MSC therapy in hydatid cyst disease.

Challenges such as the variability in MSC quality, quantity, regulatory landscape, economic, and logistical challenges must also be addressed to advance MSC therapy towards clinical application. Collaboration between researchers, clinicians, and regulatory agencies, may offer MSC therapy as a safe and effective treatment option for patients with hydatid cyst disease. Ultimately, improving the quality of life and reducing the burden of this disease is the main goal of this study on global health.

Declarations

Competing interests

The authors have declared no conflicts of interest.

Authors' contributions

Amir Mohammad Abbasi, Mohammad Reza Eftekhari Hasan Abad wrote the draft of the manuscript. Muhammad Saeed revised the draft of the manuscript and check the final version of the article. All authors have read and approved the final version of the manuscript for publication in the present journal.

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Ethical considerations

The authors declare that this manuscript is original and has not been submitted elsewhere for possible publication. The authors also declare that the data used/presented in this manuscript has not been fabricated.

Availability of data and materials

The authors will provide the data from the present study in case of request.

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